Amendments to the Drawings

Please replace Table 3 at page 143 with amended Table 3 provided herewith.

Remarks

Courtesies extended to Applicants' representative during the telephone interview held October 24, 2006, are acknowledged with appreciation.

By the present communication, claims 1, 2, 4, and 7 have been amended. No new matter is introduced as the claimed subject matter is fully supported by the specification and claims as originally filed. In view of the amendments submitted herewith, claims 1-25 are pending, with claims 1-9 under active prosecution. Amendments submitted herewith are not to be construed as a dedication of the subject matter not presently claimed to the public. Applicants reserve the right to pursue claims as originally filed in a continuation application. The Listing of Claims with appropriate status identifier begins on page 4 of this communication.

The Title is amended to refer to a method of using phosphodiesterase 5A to focus on the subject matter of the elected claims. The Abstract is amended to include the complete name of the enzyme, phosphodiesterase 5A. Paragraph **[0083]** is amended to include reference to SEQ ID NOs for the amino acid sequences of Table 1. Paragraph **[0323]** is amended to correct the alignment of the equation provided.

Claim 1 is amended to define the invention with greater particularity. The preamble is amended to include the term "improved" before "ligand", which finds support, for example, in specification paragraph **[0031]**. Line 5 is amended to change "co-crystals" to "a co-crystal", which finds support, for example, in specification paragraph **[0078]**. Line 7 is amended to change "molecular scaffolds" to "at least one molecular scaffold", consistent with line 5. The claim is also amended to include the step of testing the ligand for binding to PDE5A, wherein binding with increased affinity or specificity indicates an improved ligand. This finds support, for example, in specification paragraphs **[0029]** and **[0031]**.

Claim 2 is amended to change the characterization of the molecular scaffold from "is a weak binding compound" to "binds to the binding site of PDE5A with a dissociation constant of

1 μM to about 1 mM," support for which is found, for example, in specification paragraphs **[0183]-[0184]** and the claims are originally filed.

Claim 4 is amended to define the invention with greater particularity. The preamble is amended to include the term "improved" before "ligand", which finds support, for example, in specification paragraph **[0031]**. The claim is also amended to include additional steps of determining the orientation of the compound in a co-crystal, identifying chemical structure of the compound and modifying one or more of these structures to provide a derivative of the compound. This finds support, for example, in specification paragraphs **[0017]** and **[0029]**. Line 9 is amended to change "a derivative" to "the derivative", consistent with introduction of the term "derivative" in an earlier step, and the claim is further amended to indicate the derivative binds with greater specificity, as supported, for example, in specification paragraph **[0026]**.

Claim 7 is amended similarly to claim 2, replacing "binds weakly to said plurality of phosphodiesterases" with "binds to said plurality of phosphodiesterases with a dissociation constant of 1 μM to about 1 mM," support for which is found, for example, in specification paragraphs **[0183]-[0184]** and the claims as originally filed.

By the present communication, there is provided replacement Table 3. Table 3 as originally filed was rendered in color to identify residues conserved between various members of the aligned set of phosphodiesterase domains for several phosphodiesterases. See paragraph **[0085]**. Applicants believe that the graphical reproduction quality of Table 3, as judged by inspection of the Image File Wrapper in the PAIR system, is enhanced by rendering in gray scale. Accordingly, in Table 3 as amended, yellow residues (original) have been shaded gray, and red residues (original) have been shaded gray and boxed. No new matter is added by the replacement of Table 3.

In view of the preceding amendments and the remarks made herein, the present application is believed to be in condition for allowance.

Compliance with Sequence Rules

The Office Action indicates that the application contains sequence disclosures that fail to fully comply with the requirements of 37 C.F.R. 1.821 through 1.825. The Office Action indicates that the structural coordinates of Table 1 require introduction of SEQ ID NO. label(s) either in the description of the table or in the Figure directly. Applicants have amended the specification paragraph **[0083]** and provided an updated Sequence Listing to include the appropriate SEQ ID NOs for this table. The Office Action also indicates that Tables 1-4 disclose amino acid and/or nucleic acid sequences that must comply with sequence rules. Table 1 has been corrected as discussed. For Tables 2-4, the Examiner's attention is directed to the fact that a Sequence Listing and amendment to the specification were filed on October 19, 2004. The amendments submitted at that time include amendment of paragraphs **[0084]**, **[0085]**, and **[0086]**, inserting SEQ ID NOs for the sequences provided in Table 2, Table 3, and Table 4, respectively. Applicants believe that with these amendments, the specification is in compliance with sequence listing requirements.

Objections to the Specification

The Office Action indicates on pages 4-6 that the specification is objected to for various informalities, as follows:

a. The specification is objected to because the title is allegedly not descriptive of the elected claims. The title has been amended per Examiner's suggestion to read "Method of Using a Phosphodiesterase 5A (PDE5A) Crystal Structure for Development of Ligands".

b. The Abstract is objected to for allegedly not completely describing the disclosed subject matter. The Examiner suggests the inclusion of the name of the enzyme (phosphodiesterase 5A) and the source (human kidney) for completeness. Applicants have amended the Abstract to spell out the full name of the subject enzyme, phosphodiesterase 5A, prior to the first occurrence of the abbreviation therefore, PDE5A (amended to be in parentheses). As discussed during the

telephone interview, Applicants believe that the source is not necessary in the Abstract, as the enzyme itself is sufficient to define the disclosed subject matter.

c. The Office Action alleges that the term PDE5A, used for the catalytic domain of PDE5, does not provide which residues are considered as the catalytic domain. As discussed during the telephone interview, Applicants respectfully disagree, as the meaning of the catalytic domain of PDE5A is known in the art, and it is not necessary to provide any residues.

d. The denominator of equation for Ki on pp. 92 is not correctly aligned. Applicants have amended paragraph **[0323]** to provide proper alignment of this equation.

e. The specification is objected to for allegedly not being in the appropriate format/title sections required by MPEP § 600, suggesting that the "Brief Description of the Drawings" should be prior to the "Summary" section. As discussed during the telephone interview, Applicants believe this is mistaken, as MPEP § 601 I. under "*Arrangement and Contents of the Specification*", indicates the preferred order of ...(E) Background of the invention...(F) Brief summary of the invention...(G) Brief description of several views of the drawing. This is the order these sections appear in Applicants' specification.

f. The specification is objected to for the alleged interchangeable use of the terms "comprising", consisting essentially of" and "consisting of" in the instant application pp. 97, paragraph **[0342]**. The Office Action further states that this definition is repugnant to the art where MPEP § 2111.03 clearly defines the scope of each of these terms. Applicants respectfully disagree with this assessment of the instant specification. As discussed during the telephone interview, where the specification in paragraph **[0342]** indicates at lines 3-5 "[t]hus, for example, in each instance herein any of the terms "comprising", "consisting essentially of" and "consisting of" may be replaced with either of the other two terms", this does not mean that the meanings of these terms are interchangeable, but that for an embodiment of the invention using one of the terms, the invention also includes another embodiment wherein one of these terms is replaced with another of these terms. In each embodiment, the terms have their established meaning.

Thus, for example, one embodiment may encompass a process comprising a series of steps, another embodiment would encompass a process consisting essentially of the same steps, and a third embodiment would encompass a process consisting of the same steps.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-9 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action alleges that the use of the terms "comprising", "consisting essentially of" and "consisting of" can be used interchangeably by the instant specification pp. 97, paragraph **[0342]**, and that this implies claims with said three terms have the exact same scope. Applicants respectfully disagree with this assessment of the instant specification. As discussed during the telephone interview, where the specification in paragraph **[0342]** indicates at lines 3-5 "[t]hus, for example, in each instance herein any of the terms "comprising", "consisting essentially of" and "consisting of" may be replaced with either of the other two terms", this does not mean that the meanings of these terms are interchangeable, but that for an embodiment of the invention using one of the terms, the invention also includes another embodiment wherein one of these terms is replaced with another of these terms. In each embodiment, the terms have their established meaning. Thus, for example, one embodiment may encompass a process comprising a series of steps, another embodiment would encompass a process consisting essentially of the same steps, and a third embodiment would encompass a process consisting of the same steps. Applicants believe that no correction is necessary and respectfully request withdrawal of the rejection.

Claims 1-3 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action alleges that the method claim is missing a critical method step to achieve the claimed invention (i.e. screening, assaying to identify a ligand) and that clarification is required. While Applicants respectfully disagree with this assertion, in

order to reduce the issues and advance prosecution, Applicants have amended claim 1, without prejudice, and reserve the right to pursue claims as originally filed in a continuation application. The amended claim adds the term "improved" to the preamble, such that the claim is directed to a method of developing "improved" ligands which requires, *inter alia*, testing the modified scaffold molecule to determine whether such compound is an improved ligand. Applicants believe claim 1 as amended, and dependent claims 2 and 3 particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicants respectfully request withdrawal of the rejection.

Claims 2 and 7 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action alleges that in the terms "weak binding" or "binds weakly", "weak" or "weakly" is a relative term, that the terms are not defined by the claim, and that the specification does not provide a standard for ascertaining the requisite degree, such that one skilled in the art would not be reasonably apprised of the scope of the invention. While Applicants respectfully disagree with this assertion, in order to reduce the issues and expedite prosecution, Applicants have amended claims 2 and 7, without prejudice, and reserve the right to pursue claims as originally filed in a continuation application. The claims have been amended to expressly indicate binding with low (i.e., K_d 1 μM to about 100 μM) or very low affinity (i.e., K_d about 100 μM to about 1 mM). Applicants point out that in paragraph **[0184]** of the specification, binding with low affinity, very low affinity and extremely low affinity are expressly defined, i.e., as binding with K_d above 1 μM, 100 μM and 1 mM, respectively, such that binding with low or very low affinity would encompass compounds with K_d of 1 μM to about 1mM. Applicants believe the claims as amended particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully request withdrawal of the rejection.

Claims 4-9 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. The Office Action alleges that the term "derivative" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention, and further indicates that it is unclear how similar the derivative must be to the initial compound. Applicants respectfully disagree with this rejection. As discussed during the telephone interview, Applicants point out that the term "derivative" is expressly defined in Applicants' specification. See, for example, paragraph [0021] of the specification, where "derivative" is defined to include "...a chemical structure that contains a common core chemical structure as a parent or reference compound, but differs by having at least one structural difference...". The claims at issue are directed to a method of developing a ligand, where one of skill in the art could readily carry out the steps required by the claim, i.e., identify a compound that binds to a plurality of phosphodiesterases, make and test derivatives of the compound, and thereafter determining if they have the desired property of binding to PDE5A with greater specificity. It is irrelevant how similar the derivative must be to the initial compound, this is determined by practicing the method. Applicants respectfully request withdrawal of this rejection.

Rejection under 35 U.S.C. § 112, first paragraph, written description

Claims 1-3 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office Action alleges that the claims contain subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the art that then inventors, at the time the application was filed, had possession of the claimed invention. In the paragraph bridging pages 9-10 of the Office Action, it is further alleged that:

> The instant specification teaches a method for developing ligands to PDE5A using the three-dimensional coordinate of PDE5A disclosed in Table 1. However, the breadth of the claims includes a method for developing ligands by any possible PDE5A co-crystal structure coordinate. The instant specification teaches only one species of method for developing ligands using coordinates of Table 1. The prior art also teaches one species of

method for developing ligands using the coordinates of Saccharomyces cerevisiae YKG9 protein disclosed by Ho et al. (2000). However, the specification and the prior art do not teach sufficient correlations between a structure of PDE5A co-crystal and a function of binding site residues. Because of the lack of correlation between structure and function and the claimed genus cannot be represented by the disclosure of instant specification, one skilled in the art would not be in possession of the claimed genus inventions by the instant specification.

Applicants respectfully disagree with this rejection. Specifically, as discussed during the telephone interview, Applicants disagree with the assessment of Ho et al. as teaching a method of developing ligands. The reference makes no mention of ligand development of any kind, but is instead directed to studying GAF domain structures and binding of cGMP in various proteins, using the non-PDE protein YKG9 as a model for the GAF domain of PDE5. Claim 1, as currently amended, is drawn to a method for developing improved ligands for PDE5A, wherein a molecular scaffold that binds to PDE5A is identified, the orientation of the molecular scaffold in a co-crystal with PDE5A is determined, chemical structures of the molecular scaffold are identified and modified, and the resulting potential ligand is assessed for binding to PDE5A to determine if an improved ligand is formed. Applicants have provided substantial description of a protocol to follow in developing such ligands, where the specific example provided using the coordinates of Table 1 demonstrates to one skilled in the art how to follow this protocol. Applicants have provided an example of a suitable co-crystal, and have described how to use the information from such a co-crystal. Information from any co-crystal could be suitably used to develop ligands according to Applicant's disclosure.

Applicants provide an example of a method of obtaining the necessary structure of the co-crystal, where such structure provides adequate information to determine whether the compound in the co-crystal is suitably bound such that Applicants' method of ligand development may be applied. That the method is focused on a well known sub-class of phosphodiesterase, i.e. PDE5A, provides one of skill in the art with substantial information about the expected structure. Based on this information, taken together with the disclosure of Applicants' example, one skilled in the art would expect to find similar structure(s) with a compound in the catalytic site of other

PDE5A co-crystals. The art concerning the PDE5A catalytic domain, as exemplified in Applicants' co-crystal, is sufficient to assess the data from any PDE5A co-crystal and apply this to Applicants' method as appropriate. Applicants' invention, as fully described, is to take the information from any PDE5A co-crystal, determine the orientation of the compound in the PDE5A, and modify a structure on the compound accordingly, where such process could be applied to any appropriate co-crystal of PDE5A, where the binding site interaction of the compound in the co-crystal is determined from the co-crystal structure. All that is necessary, and clearly in Applicants' possession, is the orientation of the compound as determined by the PDE5A co-crystal structure and identification of appropriate structures on the compound that can be suitably modified to develop improved ligands, which may be applied to any appropriate PDE5A co-crystal. Applicants respectfully request that this written description rejection be withdrawn.

Claims 5-6 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office Action alleges that the claims contain subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. In the paragraph bridging pages 11-12 of the Office Action, it is further alleged that:

> The instant specification teaches a method for developing ligands to PDE5A. However, the breadth of the claims includes a method for developing all compounds having 10-fold greater specificity toward PDE5A compared to other PDE. The instant specification teaches several species of compounds in pp. 93 without disclosing any assay results. The prior art teaches a method of developing ligands by disclosing an inhibitor compound Zaprinast, for example, in pp. 4718 Table 1 of Rascon et al. (2002), which has more than 10 fold greater specificity toward PDE5 compared to TbPDE2B. Therefore, the specification and prior art do not teach sufficient correlations between a structure of compounds and function of having greater than 10 fold specificity. Because the lack of correlation between structure and function, and the claimed genus cannot be represented by the disclosure of instant specification, one skilled in the art would not be in possession of the claimed genus invention by the instant specification.

Applicants respectfully disagree with this rejection. Applicants disagree with the assessment of Rascon et al. as teaching a method of developing ligands. As discussed during the telephone interview, the reference is directed to PDE structures and interactions with inhibitors, including screening for activity, but does not provide a method of ligand development. Applicants point out that lack of correlation between structure and function are irrelevant to the written description requirement. Applicants have provided adequate description of the claimed method, providing structure to the compounds by their ability to bind phosphodiesterase (readily determined as exemplified by Applicants), and by the ability to modify structures to provide ligands with greater specificity. Applicants have provided exemplary species that could be used as molecular scaffolds for the process, and adequate description of how to modify the compounds and determine the activity of the resulting ligands. The Office Action has failed to provide adequate reason why one skilled in the art would not recognize that Applicants were in possession of such invention. Applicants respectfully request the written description rejection be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph, enablement

Claims 1-3 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for a method for developing a ligand binding to PDE5A by the three-dimensional coordinates of Table 1, however, allegedly does not reasonably provide enablement for a method of developing ligands binding to PDE5A by any other three-dimensional coordinates representing all possible conformational variation of PDE5A. The Office Action further alleges (see lines 6-18 at page 13 of the Office Action):

> The nature of the invention is drawn to a method for developing ligands binding to PDE5A by any three-dimensional coordinate of PDE5A-ligand co-crystals. The breadth of claims 1-3 is broad as to encompass a method of using any possible PDE5A co-crystal structure. However, the specification and prior art do not disclose sufficient working examples for enablement of genus method. The specification provides only one working example of a method using PDE5A coordinates provided by the Table 1. The prior art also discloses one working example of a method for developing ligands binding to PDE5A by Ho et al. Because the direction and guidance are insufficient, making

ligands binding to PDE5A is unpredictable by a claimed genus method. By all the reasons above, the quantity of experimentation needed to make or use the invention claimed based on the content of the disclosure is very high thus requiring undue experimentation for a skilled artisan to make and use the entire scope of the claimed invention.

As discussed above, and during the telephone interview, Applicants disagree with the assessment of Ho et al. as teaching a method of developing ligands. The reference makes no mention of ligand development of any kind, but is instead directed to studying GAF domain structures and binding of cGMP in various proteins, using the non-PDE protein YKG9 as a model for the GAF domain of PDE5.

While Applicants respectfully disagree with the assertions set forth above, in order to reduce the issues and expedite prosecution, Applicants have amended claim 1, without prejudice, and reserve the right to pursue claims as originally filed in a continuation application. Applicants' claims 1-3 are directed to the development of a ligand to PDE5A. The invention uses a co-crystal of PDE5A with a compound (i.e. molecular scaffold) in determining the orientation of the compound within PDE5A. Such a co-crystal is, therefore, a precondition to carrying out the claimed method. If no such co-crystal exists, one would not apply the invention method. If, on the other hand, such a co-crystal were available, one of skill in the art could readily carry out the invention method. A chemical structure of the compound is then modified to provide a potential ligand, which is then tested for binding to, or activity against, PDE5A, and possibly other phosphodiesterases, such that those potential ligands with either higher activity against PDE5A or binding to PDE5A with greater affinity or specificity, or both relative to the compound are provided as ligands. The exemplary co-crystal and described methods of making such crystals should not limit the scope of these claims. One skilled in the art is fully enabled to use such co-crystal data to develop ligands according to Applicants' disclosure. Applicants' claims are directed to what is done with the information from the crystal once formed, which is fully enabled by the example provided.

Applicants do not claim crystallization of any and all PDE5A with suitable compounds, rather, Applicants claim a method of using such crystals once they are formed. There is adequate disclosure to enable one skilled in the art to take an appropriate PDE5A polypeptide and compound and screen for appropriate crystallization conditions, analyze any resulting crystals, and to determine the orientation of the compound in the co-crystal. There is adequate disclosure to enable one skilled in the art to appropriately modify the compound to provide potential ligands, and to enable one skilled in the art to assess the activity of the potential ligand. The disclosure fully enables one skilled in the art to assess compounds for binding to PDE5A in order to identify a molecular scaffold, to prepare appropriate co-crystals, to assess the structure of the compound in the binding site, and to further modify the compound, and test the resulting derivatives for improved ligands. The improved ligands are selected based on the results of testing for defined properties, e.g., the activity of the resulting compounds. Thus, the claim is directed to a method of developing such ligands, and following the claimed process will provide such selected ligands.

Applicants respectfully disagree with the Office Action assertion that "[b]ecause the direction and guidance are insufficient, making ligands binding to PDE5A is unpredictable by a claimed genus method". Applicants have provided sufficient guidance, and it is that very guidance as to how one of skill in the art would carry out the invention method that provides some predictability to making the desired ligands. One skilled in the art is fully enabled to obtain and use a co-crystal in order to determine the orientation of a compound in the co-crystal, identify appropriate chemical structures on the compound, and make new compounds to be assessed for their binding to PDE5A. As such, the identifying of appropriate chemical structures to modify accordingly effectively provides predictability to the method of making the ligands.

The Office Action assertion that the quantity of experimentation is "very high thus requiring undue experimentation for a skilled artisan to make and use the entire scope of the claimed invention" is not a valid conclusion. Based on Applicants' disclosure, the experimentation necessary to develop such ligands is not undue. A large quantity of

experimentation is not necessarily undue experimentation if the art demands such large quantities. It is by mere routine experimentation that one skilled in the art can provide the appropriate PDE5A protein and compounds to use in screening for appropriate crystallization conditions, for example using a screening kit as described in specification paragraph **[0052]**. Moreover, Applicants' claimed method is not predicated on the success rate of such screening, only on taking the resulting information from the co-crystal and developing PDE5A ligands. Further, determining the orientation of the compound, identifying chemical structures and modifying them are a matter of routine experimentation in the art. The invention method is a sophisticated integration of several arts, such as crystallography, molecular biology, informatics, biochemistry and chemistry, such that all of the necessary experimentation is routine to these skilled artisans collectively.

Applicants believe that adequate direction and guidance has been provided to fully enable the invention as presently claimed. Regarding the method step of identifying a molecular scaffold compound that binds to a binding site of PDE5A, specification paragraph **[0182]** provides an example of how such scaffolds may be identified, with the subsequent paragraphs **[0183]-[0210]** providing various methods for assessing the binding of compounds to proteins. Further, Examples 10 and 11 (specification paragraphs **[0320]-[0325]**) demonstrate methods specific to phosphodiesterases, including PDE5A.

Regarding the step of determining the orientation of the molecular scaffold in a co-crystal with PDE5A, the specification provides adequate disclosure of how to grow crystals and determine structure (paragraphs **[0117]-[0140]**), with Examples 3-4 (paragraphs **[0317]-[0319]**) and Table 1 providing a specific example using PDE5A. Also, Examples 1 and 2 (paragraphs **[0311]-[0316]**) exemplify cloning and purification of PDE5A, using methods well known to those of skill in the art, which could be readily applied to any PDE5A sequence or other PDE sequence, which could be used in identifying suitable scaffolds or in preparing co-crystals.

Regarding the step of identifying chemical structures of the molecular scaffold that, when modified, alter the binding affinity and/or binding specificity between the molecular scaffold and PDE5A, specification paragraphs **[0238]-[0241]** adequately describe the identification of such chemical structures, where the subsequent step of synthesizing a test compound by modification of such chemical structures is readily known to one skilled in the art of organic chemistry, as discussed in specification paragraph **[0266]**.

Finally, the step of testing the modified compound for binding to PDE5A with increased affinity and/or specificity can be readily carried out by one skilled in the art, for example using the screening methods discussed above for the first step of identifying a molecular scaffold. As each step is fully enabled to one of skill in the relevant art, the method as a whole is fully enabled. Applicants respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. § 102(b)

Claims 1-9 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Ho et al. The Office Action alleges (see the paragraph bridging pages 14-15 of the Office Action):

> Ho et al. teach a method of developing ligands by disclosing a co-crystal structure model of cyclic-GMP(cGMP)-PDE5-GAFa motif in Fig. 7A and close up view of cGMP binding site of the PDE5 in Fig. 7B (see pp. 5295 left column). Ho et al. also disclose three previously known active site residues are "located on conserved core structures and can therefore be pinpointed reliably in the modeled structure of PDE5-GAFa" (see pp. 5293, bottom of left column). The cGMP in the co-crystal structure of Ho et al. was "manually docked" (see description of Fig. 7(b)) thus serve as molecular scaffold for PDE5A. Ho et al. also disclose "PDE5 and PDE6 are highly specific for cGMP as substrate, while PDE2 hydrolyzes both cAMP and cGMP" thus disclosing a modified molecular scaffold, which is cAMP, having altered affinity and/or binding specificity as disclosed in the instant claims. The molecular scaffold cGMP of Ho et al. binds to a plurality of phosphodiesterase PDE 5, 6 and 11 (see middle of right column, pp. 5288). The instant specification defines the term "binds" (pp. 11 §0024) as "interaction between a target and a potential binding compound" and have preferably "a dissociation constant (k_d) of 1 mM or less". Ho et al. teach the "GAF domain of phosphodiesterase 5 binds with K_d = 650 nM" with cGMP (see Abstract). Ho et al. also teach a method of developing compounds from a molecular scaffold (i.e. cGMP or cAMP), which interact

with several key active site residues by identifying active site residues (see Fig. 7(B) and brief description, pp. 5295). Thus Ho et al. teach all the claim limitations as disclosed in Claims 1-9.

Applicants respectfully disagree with this rejection and strongly disagree with this assessment of Ho et al. As discussed during the telephone interview, Ho et al. makes no mention of ligand development of any kind, but is instead directed to studying GAF domain structures and binding of cGMP in various proteins, using the non-PDE protein YKG9 as a model for the GAF domain of PDE5. There is absolutely no disclosure of Applicants' method steps for providing an improved ligand. The reference indicates binding of cGMP and cAMP to various PDE proteins. Assuming that cGMP could or would be used as a molecular scaffold, the mere fact that cGMP and cAMP, natural substrates to these enzymes, bind with different affinities does not suggest a method that includes the steps of identifying a chemical structure on the cGMP that can be modified to alter binding to PDE, and subsequently modifying such structure to provide a ligand such as cAMP. Ho et al. simply discloses compounds that bind to PDE, this does not suggest that cGMP and cAMP represent a molecular scaffold and modified molecular scaffold as taught by Applicants' specification and claims. Ho et al. in no way discloses all of the requirements of Applicants' Claims 1-9. Applicants respectfully request withdrawal of this rejection.

Rejection under 35 U.S.C. § 102(a)

Claims 4-9 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Rascon et al. as evidenced by Turko et al. The Office Action alleges (see paragraph bridging pages 15-16 of the Office Action):

> Rascon et al. teach a method of developing ligands by assaying PDE activities in the presence of inhibitors and each inhibition was analyzed in Table 1. Rascon et al. teach using Zaprinast which has IC_{50} of 0.76 uM and >50 toward PDE5 and Tb PDE2B, respectively. The Sildenafil (a derivative) is assayed to have an IC_{50} of 0.0039 uM and >100 toward PDE5A and Tb PDE2B thus compounds of Rascon et al. meets the limitation of having at least 10-fold greater specificity for PDE5A. Zaprinast also binds to PDE6 with IC_{50} of 0.15 uM thus meets the claim limitation of plurality (see Table 1, pp. 4718). Rascon et al. also teach the active site GAF domain of TbPDE2B "are very

similar to the two GAF domains found in mammalian PDE2, PDE5, PDE6, PDE10, and PDE11" (see middle of left column, pp. 4718) therefor Zapranist would also interact with the active site of PDE11 as inhibitor. Zaprinast interacts with at least one conserved PDE5A active site residues because it is competitive inhibitor as evidenced by Turko et al. (see Abstract, left column). Turko et al. also teach a site-directed mutagenesis to "examine the contribution of 23 conserved amino acids in the catalytic domain of PDE5" "by the classic PDE5 inhibitor zaprinast" (see top left column, pp. 125) and the results are shown in Table 1 in page 129. Thus Rascon et al. teach all limitations of Claims 4-8.

Applicants respectfully disagree with this rejection. As discussed during the telephone interview, Applicants disagree with the assessment of Rascon et al. as teaching a method of developing ligands. Rascon et al. merely looks at the differences in binding of various compounds with various PDE proteins, but does not indicate any method of developing a ligand from such information. The only mention of development of any compounds is found on page 4719, at the end of the paragraph ending on the top right column, where it indicates "[t]he significant differences between sensitivities of trypanosomatid PDEs and their mammalian counterparts make these enzymes potentially good targets for development of selective drugs." This statement, however, in no way discloses how one might go about developing such drugs, only that PDEs would be a reasonable target to which drugs may be developed.

Moreover, in order to reduce the issues and expedite prosecution, Applicants have amended claim 4, without prejudice, and reserve the right to pursue claims as originally filed in a continuation application. The claim as amended contemplates (1) identifying chemical structures of a compound that binds a plurality of phosphodiesterases, (2) modifying such structures to provide a derivative, and (3) determining whether the derivative binds with greater specificity to PDE5A than the original compound. Rascon does not disclose any such steps. As with Ho et al., the showing of two or more compounds that bind to PDEs with different specificity, even if one of the compounds may be considered a derivative of the other, in no way suggests the claimed method. Rascon et al. does not disclose all of the requirements of Applicants' Claims 4-9. Applicants respectfully request that this rejection be withdrawn.

Conclusion

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event that any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date November 14, 2006

By _____

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Enclosures—Sequence Listing
Replacement Drawings